

Summary of Safety and Effectiveness Data
Neovanta Medical AB
STAN[®] S21 Fetal Heart Monitor

I. General Information

Device Generic Name: Obstetric Data Analyzer

Device Trade Name: STAN[®] S21 Fetal Heart Monitor

Applicant's Name and Address: Neovanta Medical AB
Lilla Bommen 1
SE-411 04 Goteborg
Sweden

Original PMA Shell Number: M990048

Premarket Approval (PMA) Application Number:

Date of Panel Recommendation:

Date of Notice of Approval to Applicant:

II. Intended Use, Indications for Use

Intended Use: The STAN[®] S 21 fetal Heart Monitor (STAN[®] system) combines standard electronic fetal monitoring and ST waveform analysis of the fetal ECG to obtain information on the impact of labor on the fetus. The STAN[®] system is intended to be used to improve the assessment of the fetal condition in labor. The fetal ECG is obtained from a single spiral scalp electrode. The STAN[®] system should only be used on a singleton fetus in vertex presentation with a gestational age greater than or equal to 36 completed weeks.

Use of the STAN[®] system is indicated when there is planned vaginal delivery and:

- there is a need for close fetal surveillance during labor, or
- there are maternal disorders and/or utero-placental dysfunction with potential adverse influence on fetal oxygen and nutritional supply, or
- there is deviation from the normal course of labor including induction/augmentation of labor.

III. Contraindications

Need for immediate delivery to avoid undue delay in situations such as:

- cord prolaps
- preterminal fetal heart rate changes

Known maternal/fetal disorder when application of a fetal scalp electrode is contraindicated, such as:

- HIV
- Infectious hepatitis
- Active herpes zoster
- Known or suspected fetal coagulation disorder.

IV. Warnings and Precautions

A listing of warnings and precautions can be found in the device labeling.

V. Device Description

Functional Components: The STAN[®] S21 Fetal Heart Monitor is a fetal heart monitoring system used during labor and delivery to measure, display and analyze the ST waveform of the fetal ECG (FECG). The STAN[®] System combines this ST waveform analysis with standard Electronic Fetal Monitoring (EFM/CTG) to provide doctors and midwives with detailed information about the fetal hypoxic situation during labor.

The STAN[®] System consists of a monitor, base unit, patient sensors and embedded application software. Fetal ECG and heart rate are measured continuously via a scalp electrode placed on the presenting part of the fetus and connected by a clip connector (leg plate) directly to the base unit. Uterine activity is measured either by an external transducer (TOCO) placed on the abdomen of the mother or by an intrauterine catheter connected to an adapter cable. A skin electrode is attached to the maternal thigh and connected to the base unit by the clip connector.

Changes in the T wave and ST segment of the fetal ECG are automatically identified and analyzed by the application software. The analysis is displayed on the monitor along with an Event log identifying ST events. This information may be stored in a magneto-optical (MO) disk or communicated to external equipment via serial ports.

The system is operator controlled with a trackball and buttons. Notes can be entered from a keyboard.

The STAN[®] S21 Fetal Heart Monitor System includes these main components:

- STAN[®] S21 Fetal Heart Monitor Main Unit including STAN[®] Application software
- STAN[®] QwickConnect Plus[™] Clip Connector
- STAN[®] T21 Toco Transducer
- STAN[®] IUPT Adapter 1
- STAN[®] K21 Keyboard
- Trolley Tr22

Device Properties: Properties of the device such as materials, colors, sizes, shapes, displays, icons, indicators and packaging have been selected and designed to be relevant to the clinical use of the device, optimization of the acquired signals, and the analysis of the ST waveform of the fetal ECG during labor.

Theory and Principals of Operation: The STAN[®] S21 Fetal Heart Monitor measures changes in the fetal ECG by analysis of the ST interval of the fetal ECG. This ST interval analysis is based on the knowledge that as the fetus is exposed to increasing amounts of oxygen deprivation, it will develop hypoxia (a decrease in oxygen content of the fetal tissues.). The fetal heart reacts to these changes of oxygen content and produces changes in the ST interval.

There are two levels of analysis of the FECG waveform being performed by the STAN[®] S21. The first is the ratio of the amplitude of the T wave to the amplitude of the QRS complex. This is called the T/QRS ratio. While the QRS amplitude remains constant, the amplitude of the T wave is increased with continued lack of oxygen resulting in an increased T/QRS ratio.

The second analysis made by the STAN[®] S21 is the slope of the portion of the FECG waveform between the S wave and the T wave, called the ST segment. In a normally oxygenated heart, the ST segment is flat and near the baseline. As oxygen deprivation occurs, the slope of the ST segment may become negative. This is called a Biphasic waveform.

The STAN[®] S21 records and displays standard electronic fetal monitoring information (heart rate and uterine activity) and the trend of the T/QRS ratio together with assessment of ST segment changes (Biphasic ST). When there are significant changes in the T/QRS ratio, a flag is presented on the display and an entry made in a log of events. This Event log can be viewed on the display.

Software: There are two major components of the STAN[®] S21 Application Software. These are the Digital Signal Processing (DSP) software and the Main (SBC) software. The DSP software is responsible for analogue signal

processing and the major part of the digital filtering in the system. The SBC software is responsible for high-level signal processing, user interaction, data presentation and system control. In accordance with the FDA/CDRH *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (May 29, 1998), the level of concern for the STAN[®] S21 system software was determined to be "moderate".

Design verification consisted of audits, design reviews, code reviews and testing at multiple levels to assure that design output matched design input. Design validation consisted primarily of testing to assure that the software operates accordingly with the intended use of the device.

VI. Alternative Practices and Procedures

Electronic fetal heart rate monitoring with the data presented on a strip chart recorder is currently the most commonly used method for assessing fetal intrapartum well-being during labor. Auscultation of the fetal heart beats and palpation may also be used to assess the fetus during labor.

Intermittent fetal scalp pH, fetal oxygen saturation, and fetal scalp stimulation are also used as measures of fetal oxygen levels during labor.

VII. Marketing History

Market Area	No. of STAN [®] S 21	Number Of Complaints	Category/Reason	Number Of Recalls
Sweden	33	19	Minor/ Trackball, MO disc, Resetting of time, fuse	0
Norway	18	8	Minor/ Toco failed, Base line	0
Denmark	6	3	Minor/ Noisy sound	0
Finland	7	9	Minor/ Recording failed (no signal)	0
United Kingdom	8	4	Minor/ Not responding at power-on	0
Germany	4	5	Minor/ Non-operating, printout problem, broken screw	0
France	5	8	Minor/ Rear fan alarm, screen went black	0
Netherlands	2	1	Minor/ Scaling incorrect, fuse blown out in printer	0
Italy	2	0		0
Belgium	3	0		0
Czech Rep	4	0		0
Poland	3	0		0
Hungary	1	0		0
Total	96			0

VIII. Potential Adverse Effects of the Device on Health

Fetal and neonatal outcomes:

The overall incidence of neonates admitted to special neonatal care in the pivotal study was 7.56% in the control group and 6.59% in the test group. The primary reasons for admittance to special neonatal care were the following: After an operative delivery (48%), for general observation only (15%), respiratory distress (13%), clinical signs associated with infections (11%), jaundice (6%), hypoglycemia (4%) and neonatal distress (2%).

Maternal Outcomes:

There were no maternal adverse events during the study that were identified as being absolutely associated with device use in the clinical study.

IX. Summary of Published Literature, Experimental Studies, Safety Testing

Published and unpublished literature has been reviewed and summarized. The review of the literature included these subjects:

- Physiological Reactions to Hypoxia
- The CTG
- The ST Waveform of the Fetal Electrocardiogram
- Assessment of the Condition of the Baby

Experimental Studies: Over 30 years of research has been conducted on the STAN[®] concept. The following charts summarize this research.

List of Animal Studies Performed

Reference: Rosen KG, Kjellmer I. Changes in the fetal heart rate and ECG during hypoxia. Acta Physiol Scand 1975;93:59-66

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1971 - 1973	Guinea-pig fetuses Cat fetuses Lamb fetuses Anaesthetised term fetuses, acutely exteriorised and subjected to graded hypoxia.	20 3 3	<p>Objectives To investigate the vagal influence on the fetal hypoxic bradycardia and to identify changes in the fetal ECG during graded hypoxia.</p> <p>Study outline The vagal influence of the fetal hypoxic bradycardia was tested by comparing the time for onset of bradycardia, with or without vagal activity.</p> <p>Precordial ECG was continuously recorded and used for FHR measurement and for identification of changes in the ECG waveform during graded hypoxia.</p> <p>Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (3-10% O₂)</p>	<p>There was no indication of any vagal component in the fetal hypoxic bradycardia. Bradycardia is therefore to be regarded as a sign of myocardial hypoxia and failing fetal circulation.</p> <p>The ECG showed that the fetal bradycardia initially is an AV-block, type II.</p> <p>The data also showed that there are progressive changes in the ST interval as an early sign of hypoxia. Both an increase in the T wave amplitude, S-T elevations and negative T waves were recorded.</p>	<p>Continuous fetal ECG recordings during hypoxia showed that the fetal bradycardia, is due to an AV-block, type II.</p> <p>There are progressive changes in the ST interval, which can serve as a most early sign of fetal hypoxia. Since the T wave represent myocardial repolarization, which is a metabolically active, energy consuming process, the rise in the T wave amplitude seen, could be a sign of rise in plasma potassium due to glycogen metabolism.</p>

Reference: Rosen KG, Isaksson O. Alterations in the fetal heart rate and ECG correlated to glycogen, creatine phosphate and ATP levels during graded hypoxia. Biol Neonate 1976;30:17-24.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1974	Guinea-pig fetuses Anaesthetised term fetuses, acutely exteriorised and subjected to graded hypoxia.	40	<p>Objectives To investigate how the depletion of glycogen, creatine phosphate and ATP in the fetal heart, liver and brain correlates with FECG changes during graded hypoxia.</p> <p>Study outline The depletion of glycogen, creatine phosphate and ATP in the fetal heart, liver and brain, were analysed in biopsy samples.</p> <p>ST interval changes were graded in a FECG scoring system, with an eight-graded scale, according to severity.</p> <p>The first fetus of each litter was immediately biopsied and served control for its littermates.</p> <p>Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (8% O₂)</p>	<p>A strong linear correlation was found between the FECG scoring system and the depletion of heart glycogen and creatine phosphate. ATP was unaffected until glycogen was severely affected.</p> <p>Bradycardia was strongly associated with failing myocardial metabolism.</p>	It is concluded that the changes in the fetal ECG pattern, could be regarded as a sign of myocardial glycogenolysis and early hypoxic stress.

Reference: Hökegård KH, Eriksson BO, Kjellmer I, Magno R, Rosén KG. Myocardial metabolism in relation to electrocardiographic changes and cardiac function during graded hypoxia in the fetal lamb. Acta Physiol Scand 1981,113:1-7.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1975-1976	Lamb fetuses Anaesthetised fetuses acutely exteriorised and subjected to graded hypoxia.	21	<p>Objectives To analyse the metabolic background of hypoxic FECG changes.</p> <p>Study outline Serial myocardial biopsies in the fetal lambs were analysed for depletion of glycogen, creatine phosphate and ATP.</p> <p>FECG changes were also correlated to the myocardial performance measured by, FHR, mean arterial blood pressure, combined cardiac output and myocardial contractility (dP/dt).</p> <p>Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (8-15% O₂)</p>	<p>During hypoxia there was a significant relationship between ST changes and depletion of myocardial glycogen. A highly significant correlation was seen between the amount of glycogen available and the increase rate in T wave amplitude. A parallelism was seen between the amount of available glycogen and fetal cardiovascular function.</p> <p>In the absence of acidosis and hypoglycaemia, the myocardium showed a remarkable good capacity to regenerate its glycogen stores during periods of adequate oxygenation.</p>	The present results demonstrate a close correlation between the severity of changes in the fetal ECG and the depletion of myocardial glycogen stores. An accumulation of lactate occurs in parallel to glycogen depletion.

Reference: Hökegård KH, Karlsson K, Kjellmer I, Rosén KG. ECG-changes in the fetal lamb during asphyxia in relation to beta-adrenoceptor stimulation and blockade. Acta physiol scand 1979,105: 195-203.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1976	Lamb fetuses Anaesthetised fetuses acutely exteriorised and subjected to graded hypoxia.	14	<p>Objective To investigate whether beta-adrenoreceptor stimulation and hypoxia exerted additive or potentiating effects of the FECG and several cardiovascular parameters. And to investigate if the hypoxic changes in the FECG could be blocked by beta-adrenoreceptor blocking agents.</p> <p>Study outline FECG changes were quantified according to a scoring system. The grades were then used for correlations with cardiovascular function; measured by FHR, mean arterial blood pressure, end diastolic pressure, blood gases, acid-base status, blood lactate and glucose.</p> <p>Beta-adrenoreceptor stimulation was induced by injection of isoprenaline (0.02 to 0.04 $\mu\text{g} \times \text{kg}^{-1} \times \text{min}^{-1}$).</p> <p>Beta-adrenoreceptor blockade was induced by injection of propranolol.</p> <p>Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (9-15% O_2)</p>	<p>Isoprenaline injection induced the same pattern of changes in FECG as previously recorded during hypoxia.</p> <p>By increasing the isoprenaline dose, an increase in the duration as well as the T wave amplitude were obtained.</p> <p>Propranolol completely abolished the FECG changes induced by isoprenaline as well as by mild hypoxia. During severe hypoxia, the FECG changes could not be abolished by propranolol.</p>	<p>The conclusion to be made is that mild hypoxia initiates the FECG changes via an activation of beta-adrenoreceptors while severe hypoxia induces FECG changes through a direct effect. Thus, progressive changes in the ST interval of the FECG during hypoxia, seem to reflect the myocardial glycogenolysis induced by an imbalance between energy yield and energy consumption.</p>

Reference: Dagbjartsson A, Herbertsson G, Stefansson TS, Kjeld M, Lagercrantz H, Rosén KG. Beta-adrenoceptor agonists and hypoxia in sheep fetuses. Acta Physiol Scand 1989,137: 291-299.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1981 - 1984	Lamb fetuses Anaesthetised fetuses acutely exteriorised and subjected to graded hypoxia.	17 controls 11 in the max group 7 in the 30 µg group 8 in the 10 µg group	Objective To test the influence of maternal beta-mimetic therapy on fetal reactions to hypoxia. Study outline Terbutaline was infused to the mother at three different dosages. In the 10 µg group the terbutaline concentration was in the therapeutic range (11-58 nmol/l). In the max and 30 µg group the terbutaline was (50-748 nmol/l) which is above the therapeutic range. Induction of hypoxia Intermittent complete occlusion of the maternal abdominal aorta.	Fetuses in the max group reacted to moderate hypoxia with excessive responses of heart rate, blood pressure, myocardial contractility and ST waveform changes. The mortality in this group was 50% compared to 12% for the controls. The 10 µg group did not have increased mortality, but the terbutaline caused an increase in myocardial workload and a negative energy balance during severe hypoxia. There was a close correlation between myocardial workload and the T/QRS ratio ($r=0.73$, $P<0.01$).	The data show that the fetal myocardial beta-receptors can be stimulated to their maximum capacity by high maternal doses of beta-agonist combined with hypoxia. Beta-agonist administration to the mother diminishes the fetal defence for hypoxia.

Reference: Greene KG, Dawes GS, Lilja H, Rosén KG. Changes in the ST waveform of the fetal lamb electrocardiogram with hypoxemia. Am J Obstet Gynecol 1982,144: 950-957.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1977 - 1979	<p>Lamb fetuses</p> <p>During general anaesthesia the mother and the fetus were catheterised and electrodes for FECG analysis were implanted subcutaneous in the fetus.</p> <p>The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.</p>	10	<p>Objectives To study the effect of hypoxia on the ECG waveform in the healthy but chronically instrumented fetal lamb and to explore the possibilities of automatic sampling and quantification of ST waveform changes.</p> <p>Study outline The ST waveform of the fetal ECG in ten chronically instrumented fetal lambs was measured from day 115 to term. Averaged ST waveforms were plotted at 5 min intervals in six fetuses for 2 to 22 days. No diurnal or other rhythms were seen.</p> <p>T wave amplitude was measured in relation to the QRS amplitude as a T/QRS ratio.</p> <p>20 hypoxia experiments were performed on seven of the fetuses between 120-139 days of gestation.</p> <p>Induction of hypoxia Hypoxia was induced for 1 to 2.5 hours at a time, by administration of a gas mixture of 7% or 9% O₂ and 3% CO₂ in N₂ to the ewe.</p>	<p>The T/QRS ratio was normally <0.30.</p> <p>Persistent T/QRS ratios between 0.32 and 0.65 preceded fetal death by some days in three fetuses and were associated with anaemia and/or hypotension in three other fetuses. In those animals hypoxia caused a further rise in the T/QRS ratio, mean from 0.48 to 0.81 and all died during labour.</p> <p>In the fetuses with normal ST waveforms there were differences in their respectively response to hypoxia, despite a similar drop in PO₂.</p> <p>In eight experiments the T/QRS ratio increased from 0.17 to 0.59 and promptly reverted to normal with normoxia. This was associated with a significant rise in mean arterial blood pressure, plasma lactate, glucose and fall in pH.</p> <p>In four experiments there was a moderate change in mean T/QRS, from 0.19 to 0.25, combined with a moderate increase in plasma lactate.</p> <p>Overall there was a strong correlation between T/QRS ratio and lactate levels.</p>	<p>These findings complement previous results in the acute fetal lamb preparation and suggests that ST waveform elevation, expressed as the T/QRS ratio, identifies a shift to anaerobic myocardial metabolism.</p> <p>No diurnal rhythms were seen.</p>

Reference: Rosén KG, Dagbjartsson A, Henriksson BA, Lagercrantz H, Kjellmer I. The relationship between circulating catecholamines and ST waveform in the fetal lamb electrocardiogram during hypoxia. Am J Obstet Gynecol 1984;149:190-195.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1979 - 1982	<p>Lamb fetuses</p> <p>Age during hypoxia experiments was 117-143 days of gestation.</p> <p>During general anaesthesia the mother and the fetus were catheterised and electrodes for FECG analysis were implanted subcutaneous in the fetus.</p> <p>The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.</p>	7	<p>Objectives To test the hypothesized relationship between the concentration of circulating catecholamines and T wave amplitude.</p> <p>Study outline The ST waveform of the fetal ECG, in seven chronically instrumented fetal lambs, was measured from day 117 to term. Averaged ST waveforms were plotted every 2 min. Blood sampling was done before induction of hypoxia and then every 20 min.</p> <p>16 one-hour experiments with induced hypoxia were performed.</p> <p>T wave amplitude was measured in relation to the QRS amplitude as a T/QRS ratio.</p> <p>Induction of hypoxia Hypoxia was induced for 1 hour at a time, by administration of a gas mixture of 7% to 9% O₂ and 3% CO₂ in N₂ to the mother.</p>	<p>The response to hypoxia was age-dependent. Fetuses below 126 days of gestation did not react with FECG changes and epinephrine surge, unless acidosis occurred.</p> <p>In more mature fetuses, hypoxia per se induced a surge of epinephrine and ST waveform changes.</p> <p>Overall there was a strong correlation between the T/QRS ratio and the levels of circulating epinephrine ($r=0.765$, $n=95$, $P<0.001$)</p> <p>During normoxia, epinephrine was undetectable (<0.1 nmol/l) in most fetuses, whereas norepinephrine showed an increase at term.</p> <p>The data includes one fetus with chronic ST waveform changes ($T/QRS >0.30$). This was related to a marked increase in plasma epinephrine in spite of normal blood gas values.</p> <p>It was also shown that oxygen concentrations had to decrease by 64% before an adrenaline surge occurred and the T wave increased in amplitude.</p>	<p>These findings complement previous results in the acute and chronically instrumented fetal lamb preparations. It suggests that changes in the ST waveform expressed as T/QRS ratio, identify a shift towards anaerobic myocardial metabolism, mediated by beta-adrenergic stimulation. Such a response seems to integrate well into the fetal reaction to hypoxia.</p>

Reference: Rosén KG, Lilja H, Hökegård KH, Kjellmer I. The relationship between cerebral cardio-vascular and metabolic functions during labor in the lamb fetus and newborn. Academic Press, London. 1985.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1980 -1982	<p>Lamb fetuses</p> <p>During general anaesthesia the mother and the fetus were catheterised and electrodes for FECG analysis were implanted subcutaneous in the fetus.</p> <p>The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.</p>	2	<p>Objectives To compare the different means of fetal surveillance with special emphasis on ST waveform analysis of the FECG during spontaneous labour in the chronically instrumented fetal lamb.</p> <p>Study outline The study presents two case reports of intrauterine death, due to fetal hypoxia.</p> <p>Somatosensory evoked EEG response (SEP), to assess the integrity of the fetal nervous system, was included in the chronically instrumented fetal lamb preparation.</p> <p>Case 1 Spontaneous labour at day 143 of gestation, 28 days postoperative.</p> <p>Case 2 Spontaneous labour at day 125 of gestation, 11 days postoperative.</p> <p>Induction of hypoxia Spontaneous stress during labour</p>	<p>Case 1 FHR was largely unaltered until the last 3 hours, and then a tachycardia occurred. Bradycardia and fall in blood pressure occurred during the last 5 min. Significant ST waveform changes occurred during the last 12 hours of labour. The T/QRS ratio increased progressively in parallel with increase in uterine activity and degree of hypoxia.</p> <p>The fetal brain maintained its functionality until the last 30 min. Brain death occurred 6 min before the last heartbeat.</p> <p>Case 2 In this less mature fetus, the T/QRS ratio increased from 0.30 to 0.80 between 14 and 9.5 hours prior to fetal death. Cortical activity as indicated by SEP was unaffected until the last 45 min.</p>	<p>These data indicates that the mature lamb fetus maintains its central nervous system integrity, until there are signs of cardiovascular collapse and that ST waveform changes were associated with intact fetal cortical activity and preceded fetal death by hours.</p>

Reference: Greene KR, Rosén KG. Long term ST waveform changes in the ovine fetal electrocardiogram: the relationship to spontaneous labor and intrauterine death. Clin Phys Physiol Meas 1989, 10: 33-40.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1977 - 1982	<p>Lamb fetuses</p> <p>During general anaesthesia the mother and the fetus were catheterised and electrodes for FECG analysis were implanted subcutaneous in the fetus.</p> <p>The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.</p>	12	<p>Objectives To study long-term changes in the FECG and the relationship between FECG changes and spontaneous labour and intrauterine death.</p> <p>Study outline An observational study where 12 catheterised animals were monitored. Three of them were monitored during spontaneous labour, six developed long-term ST waveform changes and three fetuses died during the postoperative period.</p> <p>Induction of hypoxia Spontaneous stress during labour</p>	<p>Uterine contraction was shown to, by themselves, induce increases in T/QRS ratio. If the ST elevation was normalised between contractions, the fetus seemed to compensate for the moderate hypoxia. When oxygenation was further reduced, the T wave remained elevated between contractions. During the final stage of labour, a progressive T/QRS increase was noticed. The lactate concentrations increased in parallel with the T/QRS increase.</p> <p>Long-term ST changes with T/QRS ratios >0.30 related to low haemoglobin levels and/or fetal hypotension. Subsequently, all these fetuses died during labour as compared to a 40% survival rate in fetuses showing a normal ST waveform. These fetuses displayed negative T waves as a sign of failing myocardial response to hypoxia. Death in uterus whatever the cause (bleeding, infection or spontaneous hypoxia) was always preceded by marked ST waveform changes.</p>	It is concluded that ST elevations with high peaked T waves could appear on long-term basis in fetuses with intrauterine complications.

Reference: Widmark C, Hökegård KH, Lagercrantz H, Lilja H, Rosén KG. Electrocardiographic waveform changes and catecholamine responses during acute hypoxia in the immature and mature fetal lamb. Am J Obstet Gynecol 1989 May, 160(5): 1245-1250.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1985 -1987	<p>Lamb fetuses</p> <p>During general anaesthesia the mother and the fetus were catheterised and electrodes for FECG analysis were implanted subcutaneous in the fetus.</p> <p>The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.</p>	16	<p>Objectives To investigate the changes in FECG and the release of catecholamines in fetal lambs of different maturity grades, during nonacidaemic fetal hypoxia.</p> <p>Study outline The study contained two groups of chronically instrumented lamb fetuses, an immature group (119 to 126 days, n=10) and a mature group (129 to 141 days, n=6).</p> <p>Hypoxia was induced and PO₂, pH, PCO₂, catecholamines and FECG were followed during hypoxic experiments.</p> <p>Induction of hypoxia Obstruction of maternal placental blood flow through complete obstruction of the maternal aorta for 60 seconds.</p>	<p>Both groups of fetuses had a marked fall in oxygen tension (immature 2.43 ± 0.12 to 1.46 ± 0.12 and mature 2.22 ± 0.15 to 1.11 ± 0.17 kPa).</p> <p>Oxygen saturation dropped from $48\% \pm 3\%$ to $17\% \pm 2$ in the immature group and from $49\% \pm 3$ to 15 ± 3 in the mature group.</p> <p>Only modest changes occurred in pH and PCO₂. Basal catecholamine concentration did not differ between the groups, but it increased more significantly in the mature group during hypoxia.</p> <p>An increase in T wave amplitude occurred in both groups during the latter part of occlusion.</p> <p>In the mature group a linear correlation was found between plasma epinephrine concentration and T/QRS ratio.</p> <p>Fetuses of both groups showed a marked bradycardia of similar magnitude during occlusion, but differed during recovery. The mature group had a slower acceleration of the heart rate. During bradycardia, the mature fetuses responded with a significant rise in mean arterial blood pressure.</p>	<p>The study suggests that fetal maturity has a significant influence, not only on the release of catecholamines during nonacidaemic hypoxia, but also on the cardiovascular reaction pattern and changes in the ST waveform.</p>

Reference: Widmark C, Jansson T, Lindecrantz K, Rosén KG. ECG waveform, short-term heart rate variability and plasma catecholamine concentrations in response to hypoxia in intrauterine growth retarded guinea pig fetuses. J Develop Physiol 1991,15:161-168.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1988 - 1989	<p>Guinea-Pig fetuses</p> <p>At mid term the doe was anaesthetised and one uterine artery was ligated on one side. She was then allowed to recover and pregnancy would continue until 63 days of gestation. The doe was then anaesthetised a second time.</p> <p>The fetuses were acutely exteriorised and subjected to graded hypoxia by letting the doe breath a low oxygen gas mixture.</p>	24	<p>Objectives To study the ST waveform of the FECG, short-term heart rate variability and plasma catecholamines in normal and growth retarded fetuses, during hypoxia.</p> <p>Study outline The study was done on 12 growth retarded fetuses and 12 of their normal littermates.</p> <p>FECG and short-term heart rate variability were studied during normoxia and in response to acute hypoxia.</p> <p>Blood was sampled and blood gases, acid-base status and catecholamine concentrations were analysed.</p> <p>Induction of hypoxia Hypoxia was induced by letting the doe breath a low-oxygen gas mixture.</p>	<p>The T/QRS ratio was normal and similar in both groups prior to the hypoxic periods.</p> <p>In the normal sized group, T/QRS ratio increased as a response to hypoxia. The growth retarded fetuses presented a completely different pattern. Seven out of twelve fetuses showed a biphasic ST waveform, with depression and downward sloping ST segment and negative T wave, during hypoxia.</p>	<p>The study indicates that hypoxia induced FECG waveform changes, differ between intrauterine growth retarded guinea-pig fetuses and their normal sized littermates.</p>

Safety Testing: Safety issues involved in the use of the STAN[®] system may include EMC/EMI hazards. The following chart shows the tests performed to address these issues.

<u>Test Description</u>	<u>Document Number</u>	<u>Products Tested</u>
Medical Electrical Equipment, Part 1: General Requirements for Safety, IEC 60601-1	Semko Report # SE 0009040/02, May 19, 2000	S21 Main Unit, R1A Clip Connector, version P1A Toco Transducer, version R1A Key board
EMC Test	Semko Report #0035019D, October 24, 2000	S21 System, version R2B (complete component list in report)
EMC Test	Semko report #0108007E, February 23, 2001	S21 System, version R1C, Brother Printer, Tr 21 Trolley
EMC Test	Semko report #0107204D, April 20, 2001	S21 Main Unit, version R3A, all transducers and cabling (complete component list in report)
EN 60601-1, Safety tests	Semko report #0009040/02, May 5, 2001	S21 Main Unit, version R3A and accessories

X. Summary of Prior Clinical Studies

Several clinical trials, both prospective and observational, were conducted in order to validate the STAN[®] concept and equipment. The following charts summarize these studies including results and conclusions.

List and comments on clinical trials leading up to the Swedish RCT

1. **Reference:** Arulkumaran S, Lilja H, Lindecrantz K, et al. Fetal ECG waveform analysis should improve fetal surveillance in labour. J. Perinat Med 1990, 18(1): 13-22.

Observational Study: IRB approval, informed consent

Objectives/ Protocol	Methods/materials	Patient population	Results	Comments
<p>Objective The objective of the study was to evaluate ST waveform changes during labour, using a recording technique with maternal skin as reference.</p> <p>ST waveform changes in the form of T/QRS ratios were correlated to FHR changes, Apgar scores and cord artery acid-base data.</p> <p>Clinical management FHR formed the basis for management of labour. The STAN recorder was used in parallel to a standard CTG recorder.</p> <p>CTG classification FHR recordings were classified as normal, suspicious or abnormal, according to FIGO News 1987 recommendations.</p> <p>ST waveform assessment Baseline and increases for more than 5 minutes in T/QRS ratio were considered. The upper level of normality was set to a T/QRS ratio of 0.25. Negative T wave components were considered abnormal.</p> <p>Respiratory acidemia Cord artery pH <7.15, standard bicarbonate >15 mmol/l</p> <p>Metabolic acidosis pH <7.15 and standard bicarbonate <15 mmol/l</p> <p>Perinatal asphyxia Cord artery pH <7.15 and standard bicarbonate <15 mmol/l. Apgar score <4 at 1 min and <7 at 5 min.</p>	<p>ST analyser STAN 8801</p> <p>Fetal ECG was obtained from a single spiral electrode with the reference point placed on the maternal thigh. The signal was fed via a preamplifier to a purpose built microprocessor for automatic assessment of the ST waveform.</p> <p>Average T and QRS amplitudes were calculated from 10 ECGs. The resultant quotient was calculated and plotted in analogue form.</p> <p>The ECG signal was sent to a FHR monitor in parallel to STAN.</p>	<p>Patients in labour with gest. age >34 weeks.</p> <p>Patients with antenatal risk factors were preferentially included.</p> <p>201 fetuses in vertex presentation were included.</p>	<p>Signal quality Signal quality was optimal for T/QRS measurements to be made at least every two minutes in 77% of the recordings. In the remaining 23% there were blank periods in the recordings, but since the T/QRS ratio was found to be stable, especially during first stage of labour also these recordings were included in the analysis.</p> <p>Operative interventions 27 (13%) operative deliveries for fetal distress. 14 with abnormal FHR leading to eight CS and six forceps deliveries. 13 with suspicious FHR leading to six CS and seven forceps deliveries. 11 of the 27 had T/QRS changes with average ratios >0.25. Three of the 27 had cord artery pH <7.15, all of these were identified by elevated T/QRS ratios.</p> <p>Neonatal outcome Three babies with clinical evidence for asphyxia. One of these had abnormal FHR trace and was delivered with CS. The other two had suspicious FHR trace. All three cases had T/QRS elevations >0.25. Five babies with metabolic acidosis. All five had T/QRS ratios >0.25 during first stage of labour.</p> <p>There were eight babies with respiratory acidemia. Five of those had abnormal T/QRS ratios in beginning of last stage, one showed no ST changes (pH=7.14), two showed increased T/QRS ratios 20 min before delivery. In one case a seven-minute bradycardia occurred (FHR <100beats).</p>	<p>The available data showed that: It is possible to use the described STAN system for on-line recording of the unfiltered fetal ECG waveform and to analyze the ST waveform.</p> <p>Acute hypoxia was recognized by a rapid rise in the T/QRS ratio.</p> <p>Changes in the ST interval are related to metabolic events in the myocardium and FHR changes relate to neuro-physiological responses during hypoxia. In other words two different parameters, identifying different responses to fetal hypoxia. The value of combined studies of FHR and ST waveform analysis was illustrated by the data.</p> <p>T/QRS ratio is less sensitive to identify respiratory acidosis. Respiratory acidosis though, is not a major threat to the baby.</p> <p>T/QRS ratio <0.25 identifies with 99.3% accuracy a fetus with normal buffering capacity, independent of FHR tracing. Unnecessary CS could thereby be avoided.</p> <p>Because of the low rate of perinatal asphyxia and because of early interference based on FHR traces, further studies are required to evaluate whether fetal ECG waveform analysis will improve the diagnosis of perinatal asphyxia.</p>

2. Reference: Maclachlan NA, Spencer JAD, Harding K, Arulkumaran S. Fetal acidemia, the cardiotocograph and the T/QRS ratio of the fetal ECG during labor. Br. J. Obstet. Gynaecol. 1992; 99(1): 25-31

Observational Study: IRB approval, informed consent

Objectives/ Protocol	Methods/materials	Patient population	Results	Comments
<p>Objective The objective was to compare the sensitivity and the positive predictive value between CTG and elevated T/QRS ratio, with fetal acidemia during labour and at delivery.</p> <p>FBS pH <7.20 and cord artery pH <7.12 were correlated with T/QRS ratio >0.28 and CTG classification.</p> <p>Clinical management T/QRS data were not used for clinical management. FBS was collected when clinically indicated, usually to assess FHR changes.</p> <p>ST waveform assessment The mean of three T/QRS ratios before FBS (within 10 min.) or delivery (within 30 min.), was taken as representatives for the comparison with pH or neonatal outcome.</p> <p>CTG classification FHR recordings were classified as normal, suspicious or abnormal according to FIGO News 1987 recommendations.</p> <p>Acidaemia Cord artery pH <7.12</p> <p>Metabolic acidosis Cord artery pH <7.12, BDecf >12.0 mmol/l.</p>	<p>ST analyser STAN 8801</p> <p>FHR was monitored using a Copeland scalp electrode. The same electrode was used for the ECG data to a STAN monitor for on-line calculation and recording of the T/QRS ratio. Maternal skin was used as reference.</p> <p>Average T and QRS amplitudes were calculated from 30 ECGs. The resultant quotient was calculated and plotted in analogue form.</p> <p>CTG recorders HP 8031 FM6</p>	<p>113 women in labour with term fetuses (37-42 weeks). Pregnancies with abnormal CTG were preferentially included.</p>	<p>Signal quality Interpretable CTG traces within 30 min of labour were available for 93 cases. The quality of ST recordings deteriorated during second stage of labour.</p> <p>CTG versus other factors The group with suspicious and abnormal CTG showed no increase in the rate of operative deliveries or T/QRS ratio >0.28. But they did show a significant lower median cord artery pH (P<0.03 and P<0.001) respectively.</p> <p>Neonatal outcome 17 fetuses were classified as acidaemic and the median T/QRS ratio in this group was significantly higher than in the non acidaemic group (0.21 and 0.13 respectively P<0.001). 13 of the 17 acidaemic babies had a metabolic acidosis.</p> <p>CTG results 13 of the acidaemic babies had abnormal CTG traces. This corresponds to a 38% positive predictive value and 76% sensitivity.</p> <p>ST analysis results The positive predictive value for acidaemia diagnosed solely from elevated T/QRS ratio was 71% and the sensitivity was 29%. T/QRS ratio did not correlate with scalp pH, however in combination with pathologic CTG, scalp pH values of <7.25 showed a strong correlation with increasing T/QRS ratios (r=0.71, P>0.001).</p>	<p>These data confirm that CTG interpretation in clinical practice is inaccurate.</p> <p>Interpretation of CTG changes might be improved if the traces without an associated T/QRS rise could be reliably discounted as false positive.</p> <p>Much larger clinical experiments then are presently available are required before T/QRS ratio could be considered for introduction into clinical practice.</p> <p>The T/QRS ratio should be compared to the neonatal outcome. If it is found to be associated, it could be used to reduce the number of false positives and thereby the intervention rate.</p>

Comments Related to the Paper: The study by Maclachlan et al on 113 term pregnancies used Copeland scalp clip which has been shown to adversely affect not only the quality of the ECG signal but also the presentation of the different frequency components contained within the ECG. Furthermore, no recognition was made of the lag time between the end of the STAN recording and delivery, nor did the work include the assessment of ST waveform configurations, other than elevated T waves. The study showed the limitations of using only T/QRS ratio and focusing on first-stage events, trying to relate these to the outcome of labor. The study did not contain any true case of intrapartum asphyxia, i.e. cord artery pH <7.05 and extracellular fluid base deficit >12 mmol/l. The study illustrated the need for a strict protocol to be followed in the work required to assess the clinical potentials of ST waveform analysis.

3. Reference: Murphy KW, Russell U, Johnson P, Valente J. Clinical assessment of fetal electrocardiogram monitoring in labor. Br J Obstet Gynecol 1992; 99(1): 32-37

Observational Study: IRB approval, informed consent

Objectives/ Protocol	Methods/materials	Patient population	Results	Comments
<p>Objective The objective was to investigate the potential of ST waveform analysis during labour.</p> <p>Clinical management Observational study.</p> <p>ST waveform assessment Mean T/QRS ratio during one hour, at 4, 8 and 10 cm cervical dilation, was compared with CTG changes and with indices of the infant condition at birth: Apgar scores, cord artery acid-base and need for neonatal care.</p> <p>T/QRS ratio >0.25 was considered outside the normal range.</p> <p>CTG classification The CTG was classified as normal according to the Steer criteria (1989).</p> <p>Respiratory acidaemia Cord artery pH <7.12,</p> <p>Metabolic acidosis Cord artery pH <7.12, BDecf >12 mmol/l, Apgar scores <7 at 1 min.</p>	<p>ST analyser STAN 8801 prototype</p> <p>FHR was monitored using a standard scalp electrode. The same electrode was used for the ECG data to a STAN monitor for on-line calculation and recording of the T/QRS ratio. Maternal skin was used as reference.</p> <p>Average T and QRS amplitudes were calculated from 30 ECGs. The resultant quotient was calculated and plotted in analogue form.</p>	<p>86 high-risk pregnancies, with a high frequency of inductions, instrumental deliveries, etc.</p>	<p>Signal quality Of the 86 recordings, three were excluded due to poor signal quality.</p> <p>Neonatal outcome Seven infants had respiratory acidaemia. Four had a clinically significant metabolic acidosis. The most severely affected fetus was identified by T/QRS ratio >0.25, early in labour. During the last stage of labour, the T/QRS ratio decreased and biphasic ST segments were identified. One of the fetuses showed T/QRS increase but not >0.25. One was disconnected from ST analysis before the CTG trace started to deteriorate. The last fetus, with only weak signs of metabolic acidosis, was not identified by CTG or ST trace.</p> <p>Correlations No significant relation was found between the one-hour mean T/QRS and Apgar <7 at 1 min or cord artery pH <7.12.</p> <p>There was a statistical significant correlation between one-hour mean T/QRS and BDecf ($r=0.31$, $n=39$, $P<0.05$)</p>	<p>The mean one-hour T/QRS ratio was not a good predictor of low Apgar scores, but it did identify the most severely asphyxiated child. This case also indicates that it might be necessary to also identify other changes in the ST interval, apart from T/QRS ratio.</p> <p>If fetal ECG analysis should have a role in future fetal intrapartum surveillance, it might be in conjunction with CTG. Then ST analysis could be used to decrease unnecessary interventions.</p>

4. Reference: Westgate J, Harris M, Curnow JS, Greene KR. Plymouth randomized trial of cardiotocography only versus ST waveform plus cardiotocogram for intrapartum monitoring in 2400 cases. Am J Obstet Gynecol 1993: 169:1151-60.

Interventional Study: IRB approval, informed consent

Objectives/ Protocol	Methods/materials	Patient population	Results	Comments
<p>Objective The objective was to investigate if CTG + ST analysis could improve the predictive value of intrapartum surveillance compared to CTG only and thereby decrease interventions, without increased risk for the babies.</p> <p>This prospective clinical trial was divided in a CTG only and a CTG+ST arm. The traces were compared with neonatal outcome and cord acid-base data. Both at delivery and retrospectively.</p> <p>CTG arm Interpretation of CTG and management followed accepted clinical guidelines, including FBS option. In the second stage, acutely emerging ST waveform changes for > 5 min were considered as significant.</p> <p>CTG+ST arm CTG was classified according to the same clinical guidelines as in the CTG arm, but clinical management was modified based on T/QRS ratio and ST segment waveform changes.</p> <p>Metabolic acidosis Cord artery pH <7.05 and BDecf >12mmol/l.</p> <p>Birth asphyxia Cord artery pH <7.05, BDecf >12 mmol/l, Apgar scores <7 at 5 min, Active resuscitation for 4 min and problems in the postnatal period.</p>	<p>ST analyser STAN 8801</p> <p>The fetal ECG was recorded using a standard single spiral scalp electrode. Maternal skin was used as reference. The ECG signal was used for on-line calculation and recording of the T/QRS ratio based on 30 beat averaged ECG waveforms. Biphasic/negative ST waveforms were assessed by visual analysis of printed ECG averages.</p> <p>CTG recorder HP 8040A</p> <p>Personnel training All personnel were trained both in CTG classification and ST analysis before and during the study.</p>	<p>2400 high-risk pregnancies of >34 weeks of gest. with no gross fetal abnormality were included.</p> <p>Entry in either arm was decided by draw of a sealed envelope.</p> <p>CTG arm 1212 cases</p> <p>CTG+ST arm 1188 cases</p>	<p>Signal quality In 12 of the entries ST waveform analysis could not be assessed, due to poor signal quality.</p> <p>Intervention rates There was a 46% reduction ($p < 0.001$) in operative deliveries for fetal distress, without an increase in operative deliveries for other reasons. The different CTG patterns were equally distributed in both arms.</p> <p>Neonatal outcome There were more cases of metabolic acidosis (13 vs 5) and more low Apgar scores (<7) (32 vs 20) in the CTG arm. Although this was not statistically significant it showed a trend towards improved short-term neonatal outcome in the ST+CTG arm. There were (4 vs 3) cases of birth asphyxia.</p> <p>Negative ST waveforms There were six cases identified with persistent negative ST waveforms in association with an abnormal CTG trace. All were depressed at birth and required resuscitation. These six included two of the three cases of birth asphyxia in the CTG +ST arm.</p>	<p>The study showed that ST waveform analysis discriminates CTG changes in labour and that the protocol was safe.</p> <p>The results from this study confirm that the ST+CTG analysis significantly reduces interventions without having adverse effects on the neonatal outcome. Further studies are required to statistically verify the trend towards less metabolic acidosis in the CTG+ST arm.</p> <p>The retrospective analysis of data supports the trend in improved neonatal outcome.</p> <p>CTG+ST analysis does not require additional procedures and it provides continuously available information and is therefore more likely to affect appropriate and timely decision making than fetal blood sampling.</p>

Comments Related to the Paper: A retrospective analysis of the CTG showed operative deliveries for fetal distress in 2.7% of cases with normal CTG in the CTG only group, as compared with 0.3% in the STAN group. Cases with an intermediate CTG pattern had operative interventions in 19.5% and 9.6%, respectively, and with an abnormal CTG the intervention rate was 44.4% and 35.3%, respectively. 43% of operative interventions were judged unnecessary in the CTG arm as compared with 5% in the STAN arm of the trial.

There were no significant differences in the measures of neonatal outcome, but fewer low 5 minute Apgar scores and less metabolic acidosis in the ST + CTG arm were apparent, and there was also a significant reduction in the use of fetal blood sampling. 18% of abnormal traces in the CTG arm should have had an intervention (2 cases of asphyxia) as compared with 9% in the STAN arm (1 case of asphyxia).

Three patterns of ST + CTG change occurred:

ST persistently raised, CTG normal

In this group the mean cord artery pH of 7.28 was significantly higher than all the other groupings. We believe the slightly raised ST waveform reflects sympathoadrenal stimulation from the general arousal of labor and the neonatal outcome in these cases was excellent.

ST wave form rising, CTG abnormal and deteriorating

The ST waveform became raised and the CTG abnormal and deteriorated in a group of fetuses with significantly lower mean cord artery pH (7.05; 7.02- 7.08) and higher base deficit (7.6 mmol/l; 6.1-9.1) than all the other groups; still with a normal outcome. We believe this represents fetuses that were developing a metabolic acidosis as a result of significant hypoxia.

ST Segment depressed with biphasic/negative T waves

The ST waveform was negative or the ST segment depressed in a small number, but all of these cases were depressed at birth requiring resuscitation and had low arterial pHs - less than 7.08 and BDecf more than 10 mmol/l (when available). Similar cases have been reported from other groups with metabolic acidosis, growth retardation or asphyxial death. These patterns are therefore entirely consistent with the animal data and do suggest a possibility of distinguishing the normal fetus suffering acute hypoxia, showing ST elevation and high T waves, from the chronically hypoxemic fetus which then suffers further acute hypoxic insult showing negative/biphasic ST waveforms. The 3 fetuses in the CTG+ST arm that was clinically affected, all had ST events that were not recognized by the operator. This finding focused developments on an automatic assessment of ST events and the new STAN S 21 unit was thus designed on the basis of the experience earned during the Plymouth RCT.

Benefits from ST waveform monitoring:

1. The ST waveform provides another physiological variable from the same scalp electrode used to obtain the fetal heart rate.
2. ST waveform change reflects the metabolic events occurring at a tissue level in response to compensatory mechanisms for oxygen lack in a vital central organ. All the evidence from animal data and human studies so far suggest these changes occur before there is any tissue damage.
3. The use of the CTG alone results in much unnecessary and inappropriate intervention. The sensible use of ST waveform in combination with CTG, results in a significant and safe reduction in this intervention.
4. The physiology of ST waveform change is better understood than fetal heart rate change and its use is a good way to introduce clinicians to the complex physiological responses, which occur in labor and thereby improve their interpretation of events as they affect the fetus.

Risks of ST waveform monitoring:

1. High quality signals are needed for ECG analysis and good application of a single spiral fetal scalp electrode is required. Signal noise may give erroneous T/QRS ratio results.
2. Adequate education of staff in the concepts of both ST waveform and CTG analysis is essential for correct clinical interpretation.
3. There is currently too much emphasis on the T/QRS ratio, which has the benefit of being quantifiable but is only one aspect of ST waveform assessment. It is no surprise that studies attempting to correlate T/QRS values with cord artery pH across the normal range of both parameters, hardly find any relationships at all. Important changes in the ST segment such as ST depression may be missed if the whole waveform is not examined. This examination also assesses signal quality and checks that T/QRS measurements are not erroneous as a result of noise.

5. Reference: Luzietti R, Erkkola R, Hasbargen U, Mattsson LA, Thoulon JM, Rosen KG. European Community Multi-Center Trial "Fetal ECG Analysis During Labor": ST plus CTG analysis. J. Perinat. Med. 1999; 27:431-440

Observational Study: IRB approval, informed consent

Objectives/ Protocol	Methods/materials	Patient population	Results	Comments
<p>Objective The objective was to identify changes in the fetal ECG waveform in cases of verified fetal hypoxia. In this study, the main focus was on changes in the T/QRS ratio using an automatic system for trend analysis on ST changes together with automatic identification of ECG complexes with ST segment abnormalities, i.e. ST segment depression.</p> <p>Clinical management This was a prospective study and the ECG waveform information was not available to the clinician during delivery.</p> <p>Retrospective assessment The CTG+ST traces were assessed retrospectively and blind to the clinical outcome. The data were grouped according to the CTG+ST clinical guidelines for intervention.</p> <p>Outcome parameters The outcome parameters considered were: birth weight, Apgar scores at 1, 5 and 10 min, cord artery and vein acid-base assessment, need and method of resuscitation and transferral to neonatal intensive care unit.</p> <p>ST waveform assessment The ST changes considered were; Episodic T/QRS rise (>0.10 for <10 min.), T/QRS baseline rise (>0.05 for >10 min.) and repeated biphasic STs and appearance of repeated negative T waves with ST depression. ST waveform changes were assessed different depending on the CTG classification</p>	<p>ST analyser STAN 8801 recorder connected to a PC for further signal processing, with data reduction and storage. The data was further processed to regenerate a CTG trace and a 30 beat ECG average for ST waveform analysis. The off-line signal checked for signal quality to ensure that only high quality ECG waveforms were included. T/QRS ratio was automatically calculated and ST segments with negative slopes (biphasic ST) were identified.</p> <p>ST waveform changes were identified both through visual inspections of the CTG+ST traces and through an automatic PC based algorithm, the ST Log.</p>	<p>618 cases were recorded, but due to data collection inconsistency only 320 cases could be reviewed and compared with the original case notes.</p> <p>All cases included had a gestational age of >36 weeks.</p>	<p>Signal quality. The quality of the traces allowed 84% of the available ECG to be used for FHR analysis and 80% of those for ST analysis.</p> <p>Neonatal outcome This data included six cases of intrapartum hypoxia. All were identified by ST events. One additional case had a cerebral bleeding probably associated with a ventouse delivery for failure to progress.</p> <p>CTG analysis The CTG was abnormal in 55 cases, at retrospective analysis.</p> <p>ST waveform analysis Baseline rise in T/QRS ratio occurred in five cases, all were associated with abnormal CTG. All of these neonates had evidence of intrapartum hypoxia.</p> <p>Episodic T/QRS rise occurred in 16 cases, all except one appeared in association with an abnormal CTG. All babies had an uneventful neonatal period.</p> <p>Biphasic STs were in five cases intermittent, short lasting and associated with a normal CTG. All these cases had a normal outcome. The one baby with persistent biphasic STs and an abnormal CTG, had evidence for intrapartum hypoxia.</p> <p>Operative deliveries 30 cases of operative delivery, 18 instrumental vaginal and 12 emergency CS. Operative delivery for fetal distress was performed in only two of the six hypoxic babies.</p>	<p>The strong association between ST waveform changes and adverse intrapartum events is illustrated by the fact that six out of six cases with evidence of intrapartum asphyxia showed ST changes. At the same time four of the most marked asphyxiated cases were not acted upon. Thus, there is little doubt that ST waveform analysis may add to current techniques for intrapartum fetal surveillance.</p> <p>The clinical guidelines used are based on the combined CTG +ST analysis. The latter parameter allows for a most detailed assessment of adverse events in labor associated with hypoxia.</p> <p>A new STAN recorder containing the ST log function is to be tested in a second randomised controlled trial. This study should have power enough to show, to which degree, the perinatal outcome can be improved, using CTG+ST analysis.</p>

6. Reference: ST analysis of the fetal ECG during labor improves the detection of adverse outcome data from a Nordic observational multicenter study. Beta trial (not published data)

Observational Study: IRB approval, informed consent

Objectives/Protocol	Methods/materials	Patient Population	Results	Discussion
<p>Objective As considerable improvements in signal processing occurred after the data collection for the EC multicenter trial was finalised, another retro-spective observational study, to identify changes in the ST waveform was conducted. The accuracy of the STAN clinical guidelines for inter-vention and the new ST log function was also tested. In three of the centres participating, the trial became part of the preparation for the Swedish RCT.</p> <p>Clinical management Observational study, the ST data was available to the clinician but clinical action was based on standard procedures.</p> <p>Retrospective analysis The CTG+ST traces were assessed retrospectively and blind to the clinical outcome. The data were grouped according to the CTG+ST clinical guidelines for intervention. Assessment of the clinical outcome was based on: cord artery and vein acid-base data, Apgar scores, need for resuscitation, referral to neonatal intensive care and signs of neonatal neuromuscular abnormal findings.</p> <p>ST waveform assessment The ST changes considered were; Episodic T/QRS rise (>0.10 for <10 min), T/QRS baseline rise (>0.05 for >10 min) and repeated biphasic STs and appearance of repeated negative T waves with ST depression. ST waveform changes were assessed different depending on the CTG classification.</p>	<p>ST analyser The prototype of the STAN S 21 (STAN ESST)</p> <p>ST waveform changes were identified both through visual inspections of the CTG+ST traces and through an automatic PC based algorithm called ST log.</p>	<p>574 deliveries with gestational age >36 weeks.</p>	<p>Neonatal outcome 15 cases were identified as being exposed to intrapartum hypoxia. Five of those had neonatal neurological symptoms. All five were identified as abnormal cases according to CTG+ST clinical guidelines during first stage of labour. The other ten babies had metabolic acidosis only (cord artery pH <7.05 and BDcf >12 mmol/l). Two had changes in the first stage of labour and the remaining eight showed ST changes during second stage of labour. 12 of the ST events were T/QRS baseline raises. One case displayed an episodic T/QRS increase; one case showed consistent ST depression with negative T waves and the final case had a preterminal CTG as a predominant finding with one episodic T/QRS rise.</p> <p>Eight cases had cord artery acidemia only (pH < 7.05 but BDcf <12 mmol/l). They were all unaffected at birth. Seven of these displayed CTG+ST abnormalities.</p> <p>Clinical guidelines The sensitivity for CTG+ST clinical guidelines to recommend intervention was 100% (15/15) for cases with neonatal symptoms and/or metabolic acidosis and 95.8% (22/23) when the respiratory acidosis cases were included. The corresponding figures for the specificity were 95.0% and 96.4%.</p> <p>Operative interventions The operative intervention rate according to the CTG+ST clinical guidelines was 7.5%, compared to the actual rate of 15.3%</p>	<p>The Plymouth trial showed that cases with ST elevation and abnormal CTG all had cord artery pH 7.15. In the present study, 86% of the cases where the STAN clinical guidelines called for intervention, had cord artery pH 7.15. The difference may be accounted for by the improvements in signal quality and the ability of the ST log to more accurately identify ST changes and biphasic ST patterns at an earlier stage of hypoxia.</p> <p>The experience gained this far demonstrates the ability of CTG+ST clinical guidelines, supported by computerized assessment of ST changes, to identify babies at risk of intrapartum hypoxia. Further progress of the STAN concept will depend on the outcome of the Swedish multicenter randomized controlled trial.</p>

XI. Summary of Pivotal Clinical Study and EU Project

A. Summary

Decades of dedicated research have documented a unique ability of ST waveform changes of the fetal ECG to provide accurate information the ability of the fetal myocardium to respond to the stress of labor. Recently, the second RCT of 4400 cases documented substantial improvements in perinatal outcome when standard CTG interpretation was combined with automatic assessment of ST events and a strict protocol was followed. The trial also documented the need for educational efforts and local experience. To secure accurate dissemination of the knowledge behind the STAN[®] concept, with EU support, 10 Centres of Excellence have now been established across Europe. The outcome of the initial 2181 cases showed a 0.66% incidence of cord metabolic acidosis. This low incidence is comparable with the outcome of the Swedish RCT of a reduction in cord artery metabolic acidosis rate from 1.44% to 0.57%.

B. Introduction

The aim of intrapartum fetal surveillance is to identify fetuses of an adverse outcome based on our understanding of the pathophysiology involved. ST waveform of the fetal ECG provides continuous information on the ability of the myocardium to respond to the stress of labor. An elevation of the ST segment and T wave, quantified by the ratio between T wave and QRS amplitudes (T/QRS), identifies fetal myocardium responding to hypoxia by a catecholamine surge, beta adrenoceptor activation and myocardial glycogenolysis. An ST segment depression may indicate a situation when the myocardium cannot anymore respond to hypoxia. The basis for ST waveform interpretation is given in Figure 1.

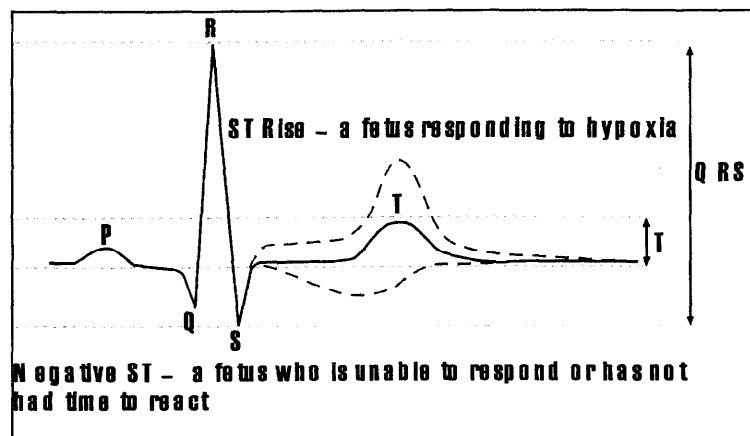


Figure 1: Principles of how to calculate the T/QRS ratio and the physiology behind different ST patterns

Strict clinical guidelines were developed and initially tested in the Plymouth RCT of CTG+ST vs CTG showing a safe reduction in operative deliveries for fetal distress (ODFD) by 46% with signs of fewer babies born with signs of intrapartum hypoxia.

The trial also showed the need to improve data presentation as three cases in the CTG+ST arm had clinical signs of asphyxia in spite of ST events, which were missed. To improve the detection of ST events, a new STAN recorder was developed utilizing modern software to improve signal quality and allow for automatic identification of significant ST events.

C. The Swedish RCT

The primary outcome of the second RCT was recently published in the Lancet showing a significant reduction in ODFD from 8.0% to 5.9% at the same time as the risk of being born with cord artery metabolic acidosis, defined as cord artery pH <7.05 and BDecf >12 mmol/l, was reduced from 1.44% to 0.57%.

The Swedish RCT was designed with a power to assess potential improvements in neonatal outcome. The trial design also allowed to test for the effects of growing experience with the new STAN[®] technology in the three busy labour ward units with cases managed by >300 midwives and physicians. The current analysis summarizes the findings associated with the 351 babies that were admitted to the Special Care Baby Unit (SCBU).

Results. Table I gives neonatal outcome according to intention to treat.

Table I. Neonatal outcome excluding lethal malformations.

	CTG		CTG+ST	
	Before n =1250	After retraining n = 1197	Before, n = 1333	After retraining n = 1186
Perinatal death	1 Asphyxia	0	1 Sepsis	1 Asphyxia

Outcome of SCBU visit

Neuromuscular symptoms				
Seizures			0	0
Increased neuromuscular tone			0	0
Irritability only			3	0
Met acid+ other symptoms			4	1
Total			8	2
OR, 95% CI, p-value				0.17, 0.03-0.7 p= 0.01

The case of intrapartum death after retraining in the CTG+ST arm had second stage CTG and ST changes that were not recognized and the scalp electrode was disconnected due to ventouse extraction for failure to progress and a severely asphyxiated baby delivered after 23 minutes. The other case had 10 minutes of T/QRS rise before a normal delivery, normal Apgar and was observed for 3 hours in

SCBU due to cord metabolic acidosis. All cases but one in the CTG+ST arm had intrapartum events detected as abnormal by the STAN[®] clinical guidelines. The case not detected had the STAN recorder disconnected 3.5 hours before delivery.

Fetal scalp pH (FBS) has hitherto been regarded as the method of reference for detection of intrapartum hypoxia. 495 cases from both arms had fetal scalp pH samples. Of a total of 46 cases with metabolic acidosis at delivery, only six had FBS data. The ST waveform could be assessed in 5 of these six babies, showing abnormalities lasting from 25 to 276 (median 119) minutes before delivery. In only one case an abnormal FBS was obtained (pH 7.13). At that point in time, ST events had been recorded for 80 minutes. In the other 5 cases, the scalp pH was normal (>7.20) and not repeated as labor progressed.

A 1600 cases interim analysis revealed six cases where ST events had been ignored and the fetus exposed to hypoxia. This observation showed that ST analysis improved the sensitivity of detecting adverse events in labor and it was decided to continue with the trial with the addition of regular staff meetings to discuss cases.

According to the protocol, a secondary analysis was made with the exclusion of neonates with severe malformations and inadequately monitored cases - those monitored for less than 20 min and cases where the monitoring was interrupted more than 20 min before delivery. Table II denotes the outcome among adequately monitored neonates during the second phase of the trial.

Table II. Neonatal outcome among adequately recorded cases during the second phase of the Swedish RCT.

	CTG		CTG+ST		OR, 95% CI, p
	n	%	n		
Total	1049		1054		
Apgar 1 min <4	23	2.19	8		0.34, 0.14-0.80, p=0.011
Apgar 5 min >7	13	1.24	8		0.61, 0.23-1.58, p=0.37
Apgar 5 min <4	5	0.48	0		p=0.031
Admissions to SCBU					0.67, 0.46-0.98, p=0.036
Cord artery metabolic acidosis	14	1.54	4	0.44	0.28, 0.08-0.92, p=0.032

Thus, irrespective of what outcome measure was applied, the Swedish RCT documented marked improvements in neonatal outcome after retraining with enhanced experience of ST analysis. The improvement in the diagnosis of intrapartum hypoxia during the second phase of the trial, also enabled a 44% reduction in ODFD from 8.7% to 5.0%, $p=0.001$.

Thus, data from two large randomized controlled trials, including 6826 cases, have shown that with the support of fetal ECG ST waveform analysis, the number of babies born with cord metabolic acidosis could be reduced from 1.43% to 0.57% (OR 0.39, 95% CI 0.21-0.72, $p = 0.0017$) at the same time as ODFD were reduced from 8.4% to 5.6% (0.65, 0.53-0.78, $p<0.001$).

D. The EU project

The expectation of society is that the application of the results of health technology assessment will improve quality of care and ensure that available resources are used effectively. The objective of the project is to develop and validate a model whereby the user aspects are put to the fore to stimulate postgraduate training and an appropriate management structure.

Today, there are no specific requirements regarding the implementation of a medical device knowledge transfer process. Action according to regulatory requirements is only required when things go wrong - obviously too late in a situation, such as labour, when oxygen deficiency may institute a threat to life and intact survival. The prime objective of the EU supported FECG project is to develop a model whereby primarily ten academic centres across Europe, as a joint effort, are made active partners of this, knowledge transfer process. These centres of excellence then become the regional hub of experience.

E. Methodology

The aim of the STAN[®] concept is to provide a more thorough understanding of fetal reactions to the stress and strain of labor. The EU supported FECG project includes the development and testing of educational material such as a trainer/simulator that allows midwives and doctors to earn their own experience from displaying real cases from our database virtually. This enables exposure to rare but important cases otherwise not easily experienced. Multi media based teaching together with conventional written material is also used. In parallel to the educational efforts, the STAN[®] S 21 fetal heart recorders are used clinically.

F. Results and discussion

Table III gives the initial data from the 10 obstetric units participating in the project.

Table III. The FECG project: Outcome of intrapartum fetal monitoring by April 1st, 2001. Corresponding data from the Swedish randomised controlled trial are also given.

	EU project incidence, (%) n = 2181	Swedish RCT incidence, (%)	
		CTG+ST n = 2228	CTG n = 2164
ODFD, STAN indication	7.2		
ODFD, CTG indication	9.1		
ODFD, Fetal scalp pH	1.3		
ODFD, total	17.6	5.9	8.0
Cord artery metabolic acidosis, (pH <7.05 and BDecf>12 mmol/l),	0.66 1921 cases with cord data available	0.57	1.44
Neuromuscular symptoms, metabolic acidosis + neonatal care	0.23	0.13	0.74

One neonate developed increased neuromuscular tone during the first 24 hours with signs of metabolic acidosis at 1h of age (no cord data available). The STAN recording showed an abnormal CTG + baseline rise in T/QRS that was missed for 60 minutes. The material includes another 13 cases with cord artery metabolic acidosis (pH <7.05 and BDecf>12 mmol/l), corresponding to 0.66%. Four of those required special neonatal care but no neuromuscular abnormalities were noted. All but one of these five cases with signs of complicated neonatal outcome had ST events lasting 20 minutes or more. Only two of the 13 cases with cord metabolic acidosis did not show ST events, nor were the CTG abnormal.

These data are comparable to those noted in the Swedish RCT. Thus, standard CTG recording would cause a metabolic acidosis incidence of 1.4%. The results achieved in the FECG project clearly indicate that the 0.6% incidence may be achieved already from the first day of STAN usage.

The primary aim of the STAN development is to reduce the risk of babies being affected by oxygen deficiency during labor. This appears to have been achieved and the work at the different centers is continuing with staff certification and more rigorous application of STAN[®] clinical guidelines together with further safe dissemination of knowledge.

XII. Risk/Benefit Analysis

Risks posed: The STAN system is basically a standard electronic fetal monitor (CTG) with the additional features of ST waveform analysis of the fetal ECG. The only change in patient handling routines, required by ST analysis, is the placement of a standard maternal thigh skin electrode.

The clinical guidelines have been tested in two randomized controlled clinical trials and found safe. The software in the STAN system has been validated clinically. Thus, risks are minimal and related to situations where no ECG signal is available. In these rare situations, no information is provided and the staff would then replace the scalp electrode and, if this fails, revert to standard electronic fetal monitoring.

Potential benefits: As stated previously, there is a need for further developments in intrapartum fetal monitoring and ST analysis has emerged through a process of dedicated research as a method to on-line assess the ability of the fetus to handle the stress of labor. As a result, operative deliveries for fetal distress and other indications has been reduced. Furthermore, the structured multi-media based teaching and training tools will stimulate staff to understand more about fetal reactions to the process of being born.

XIII. Panel Recommendations